Claims 42-55 have been added, with former claim/specification basis for these claims being found at least as follows:

claim 42 - claims 28 and 40 (as amended herein) and claim 15

claim 43 - claim 29

claim 44 - claim 30

claim 45 - claim 31

claim 46 - claim 2

claim 47 - claim 3

claim 48 - claim 4

claim 49 - claim 5

claim 50 - claim 6

claim 51 - page 51, line 19; page 18, line 3

claim 52 - page 28, lines 3-13

claim 53 - claim 13

claim 54 - page 17, line 2

claim 55 - page 16, lines 26-28

In that the amendments do not introduce new matter, their entry is respectfully requested.

Formality matters - item 4 of the Office Action

The Examiner has asked for clarification concerning whether anti-HER2 and anti-ErbB2 denote the same meaning. Applicants submit that it is clear from the specification that "HER2" and "ErbB2" are synonyms (see, e.g. page 2, line 6) and hence Applicants submit that it is permissible to use these terms interchangeably in the specification.

The new ATCC address has been added on page 51 as requested by the Examiner.

Reconsideration of the objections to the specification is respectfully requested in view of the above.

Section 112, second paragraph - item 5 of the Office Action

Claims 28-40 are rejected as being dependent on nonelected claims. In order to obviate

the rejection, claim 1 has been incorporated into claim 28 and claim 9 has been incorporated into claim 40. Reconsideration and withdrawal of the refection is respectfully requested in view of the above.

Section 102/103 - items 8 and 9 of the Office Action

Claims 28-31, 37-38 and 40 are rejected under 35 USC §102(b) as anticipated by or, in the alternative, under 35 USC §103(a) as being obvious over Shepard *et al. J. Clin. Immunol.* 11(3):117-127 (1991) or Lewis *et al. Cancer Immunol. Immunother.* 37:255-263 (1993); together "the cited references".

The Examiner states that Shepard *et al.* teaches the 4D5 anti-HER2 antibody which: (a) inhibits the growth of SKBR3 cells; (b) enhances the sensitivity of SKBR3 cells to cisplatin; and (c) enhances the sensitivity of SKBR3 cells to TNFα. The Examiner further asserts that Shepard *et al.* also teaches 7C2 and 7F3 monoclonal antibodies which bind to Domain 1 of ErbB2 and which inhibit SKBR3 proliferation by 21% and 38% respectively.

Lewis *et al.* is alleged to teach anti-HER2 antibodies 4D5, 7C2 and 7F3 which inhibit human tumor cells such as SKBR3 and mediate antibody-dependent cellular cytotoxicity (ADCC).

First, with respect to claim 28 herein, Applicants point out that the 4D5 antibody in the cited references and humanized 4D5 (recombinant human (rhu)mAb HER2 in Fig. 4 of Lewis *et al.*) do not bind Domain 1 at the amino terminus of the extracellular domain of ErbB2. See page 12, lines 28-29; Fig. 13; page 12, lines 6-13; and Fig. 13 of the present application. Hence, Applicants submit that the disclosure in the cited references concerning 4D5 or humanized 4D5 as cited by the Examiner can not anticipate the invention in claim 28.

As to the monoclonal antibodies called "7C2" and "7F3", the cited references do not disclose that those antibodies bind Domain 1 of ErbB2. Moreover, the cited references do not provide sufficient structural information concerning the 7C2 or 7F3 antibodies, such that the skilled person could have reproduced those particular antibodies based on the

teachings in the cited references. Hence, the cited references do not "make available" the 7C2 or 7F3 antibodies *per se*. Therefore, the cited references fail to teach a method for inducing cell death using an antibody which binds to Domain 1 of ErbB2.

In relation to claim 40, the 4D5 antibody in the cited references and humanized 4D5 in Lewis *et al.* do not result in about 5 to 50 fold induction of annexin binding relative to untreated cell in an annexin binding assay using BT474 cells (see Figure 8A of the present application). Therefore, the disclosure in the cited references concerning 4D5 or humanized 4D5 fails to anticipate the invention set forth in claim 40 herein.

As to the 7C2 and 7F3 antibodies, the cited references do not disclose that those antibodies result in about 5 to 50 fold induction of annexin binding relative to untreated cell in an annexin binding assay using BT474 cells. Furthermore, the cited references do not "make available" to the skilled person the particular 7C2 or 7F3 antibodies for the above reasons. Hence, the cited references fail to anticipate the method of claim 40 herein.

Applicants have shown above that the cited references fail to anticipate the invention set forth in rejected claims 28-31, 37-38 and 40. Applicants further submit that the instantly claimed methods would have been nonobvious over the cited references.

As to claim 28, there is nothing in the cited references which would suggest that Domain 1 is a useful region of ErbB2 for targeting with antibodies, much less that such antibodies can be used to induce death of a cell, such as a cancer cell, which overexpresses ErbB2. Hence, Applicants submit that the method in claim 28 would have been nonobvious over the cited references.

In relation to dependent claims 30 and 31, the cited references do not disclose a method of treating a mammal, much less a human, with the claimed antibody which binds to Domain 1 of ErbB2. With respect to dependent claims 37 and 38, the cited references fail to disclose the use of an antibody which binds to Domain 1 of ErbB2 as well as a growth

inhibitory agent or a chemotherapeutic agent in the claimed method.

Turning now to the nonobviousness of claim 40, there is nothing in the cited references which would suggest that an antibody which binds to ErbB2 and results in about 5 to 50 fold induction of annexin binding relative to untreated cell in an annexin binding assay using BT474 cells could have been made, much less that such an antibody would be useful in the method of that claim.

Hence, Applicants submit that the invention in claims 28-31, 37-38 and 40 is nonobvious over the cited references. Reconsideration and withdrawal of the Section 102 or 103 rejections based on Shepard *et al.* or Lewis *et al.* is respectfully requested in view of the above.

Section 103(a) - item 10 of the Office Action

Claims 32-36 and 39 are rejected under 35 USC §103(a) as being unpatentable over Shepard *et al.* or Lewis *et al.* in view of Fendly *et al. Cancer Research* 50:1550-1558 (1990), Deshane *et al. J. Invest. Med.* 43 (Suppl 2):328A (1995) and further in view of Senter *et al.* (US Pat. No. 4,975,278).

Shepard *et al.* is cited for teaching the 4D5 anti-HER2 antibody which: (a) inhibits the growth of SKBR3 cells; (b) enhances the sensitivity of SKBR3 cells to cisplatin; and (c) enhances the sensitivity of SKBR3 cells to TNFα. Shepard *et al.* is further cited for allegedly teaching 7C2 and 7F3 monoclonal antibodies which bind to Domain 1 of ErbB2 and which inhibit SKBR3 proliferation by 21% and 38% respectively.

Lewis *et al.* is relied upon as allegedly teaching anti-HER2 antibodies 4D5, 7C2 and 7F3 which inhibit human tumor cells and mediate antibody-dependent cellular cytotoxicity (ADCC).

Fendly *et al.* is cited for disclosing the production and characterization of the monoclonal anti-HER2 antibodies utilized by Shepard *et al.* and Lewis *et al.*

Deshane *et al.* is relied upon as purportedly teaching that intracellular antibody knockout of the ErbB2 oncoprotein achieves targeted eradication of tumor targets by induction of apoptosis.

Senter *et al.* is cited as allegedly disclosing a method for delivery of cytotoxic drugs to tumor cells using a tumor specific antibody/enzyme conjugate that binds to the tumor cells, and upon additional administration of a prodrug, the enzyme converts the prodrug to an active cytotoxic drug.

The Examiner asserts that it would have been obvious at the time the invention was made to a person having ordinary skill in the art to use monoclonal antibodies such as 4D5, 7C2 and 7F3 as taught by Shepard *et al.*, Lewis *et al.* and Fendly *et al.* to induce cell death in cells overexpressing ErbB2 by a variety of methods, one of which is apoptosis. The Examiner further contends that it would have been obvious to enhance the efficacy of the monoclonal antibodies by using the reagents and techniques taught by Senter *et al.*, or by using in concert with the monoclonal antibody treatment, radiation treatments "as widely used in the treatment of tumors".

Applicants submit that the presently claimed invention would not have been obvious in view of the cited art.

Applicants have demonstrated above that the 4D5 antibody in Shepard *et al.* or Lewis *et al.* does not (a) bind to Domain 1 of ErbB2 or (b) result in about 5 to 50 fold induction of annexin binding relative to untreated cell in an annexin binding assay using BT474 cells. Applicants have further shown above that antibodies with properties (a) or (b) are not described in Shepard *et al.* or Lewis *et al.*, and that those references do not "make available" the specific 7C2 or 7F3 antibodies.

Applicants further submit that Fendly *et al.* is similarly deficient, in that it fails to desribe antibodies with properties (a) or (b), or to sufficiently describe the structural characteristics of the anti-ErbB2 antibodies designated 7C2 or 7F3 to enable those particular antibodies.

Applicants additionally contend that the Deshane abstract fails to teach an anti-ErbB2 antibody used in the methods claimed in the present application. In particular, the ErbB2 epitope bound by the sFv is not disclosed in this abstract. Moreover, the Deshane abstract does not make available or enable an antibody which results in about 5 to 50 fold induction of annexin binding relative to untreated cell in an annexin binding assay using BT474 cells.

Senter *et al.* is silent concerning anti-ErbB2 antibodies and their properties, and fails to supply the deficiencies of the other relied-upon references concerning the presently claimed anti-ErbB2 antibodies and their uses.

Hence, Applicants submit that the instantly claimed methods would have been nonobvious over the above-cited art.

With particular reference to claim 28, Applicants contend that there is nothing in the cited art which would suggest that Domain 1 is a useful region of ErbB2 for targeting with antibodies, much less that such antibodies can be used to induce death of a cell, such as a cancer cell, which overexpresses ErbB2. Hence, Applicants submit that the method in claim 28 is nonobvious over the Examiner cited art.

With respect to claim 40, there is nothing in the cited art which would suggest that an antibody which binds to ErbB2 and results in about 5 to 50 fold induction of annexin binding relative to untreated cell in an annexin binding assay using BT474 cells could have been made. Moreover, the cited art fails to teach a method of inducing cell death using such an antibody.

Accordingly, Applicants submit that the rejected independent claims are nonobvious over the cited art.

Applicants also point out that dependent claims recite subject matter which is further not described in the cited art. For example, the cited art does not teach the advantages

associated with the combination of the Domain 1-binding ErbB2 antibody and a second anti-ErbB2 antibody which does not bind to Domain 1 of ErbB2, *e.g.* where the second antibody inhibits growth of SKBR3 cells in cell culture by 50-100% as in dependent claims 32-36. The cited art further fails to render obvious the sequencing in claim 34. See, page 58, lines 1-10; and page 59, lines 28-31 of the present application concerning the advantages associated with combining a Domain 1-binding antibody with another anti-ErbB2 antibody.

Accordingly, Applicants submit that the presently claimed invention would have been nonobvious over the cited art at the time of filing. Reconsideration and withdrawal of the Section 103 rejection is respectfully requested in view of the above.

Applicants believe that this case is now in condition for allowance, and look forward to early notification of same.

Respectfully submitted,
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